The Clot Thickens: Navigating Thrombophilia Testing and Anticoagulation Decision-Making

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Disclosures

The planners and speakers have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Learning Objectives

At the end of this session, learners should be able to:

- Recognize the pathophysiology of antiphospholipid syndrome and other types of thrombophilia and their clinical significance.
- Identify different results of thrombophilia testing.
- Outline available anticoagulation strategies in patients with antiphospholipid syndrome and other various types of thrombophilia.

Abbreviation Key

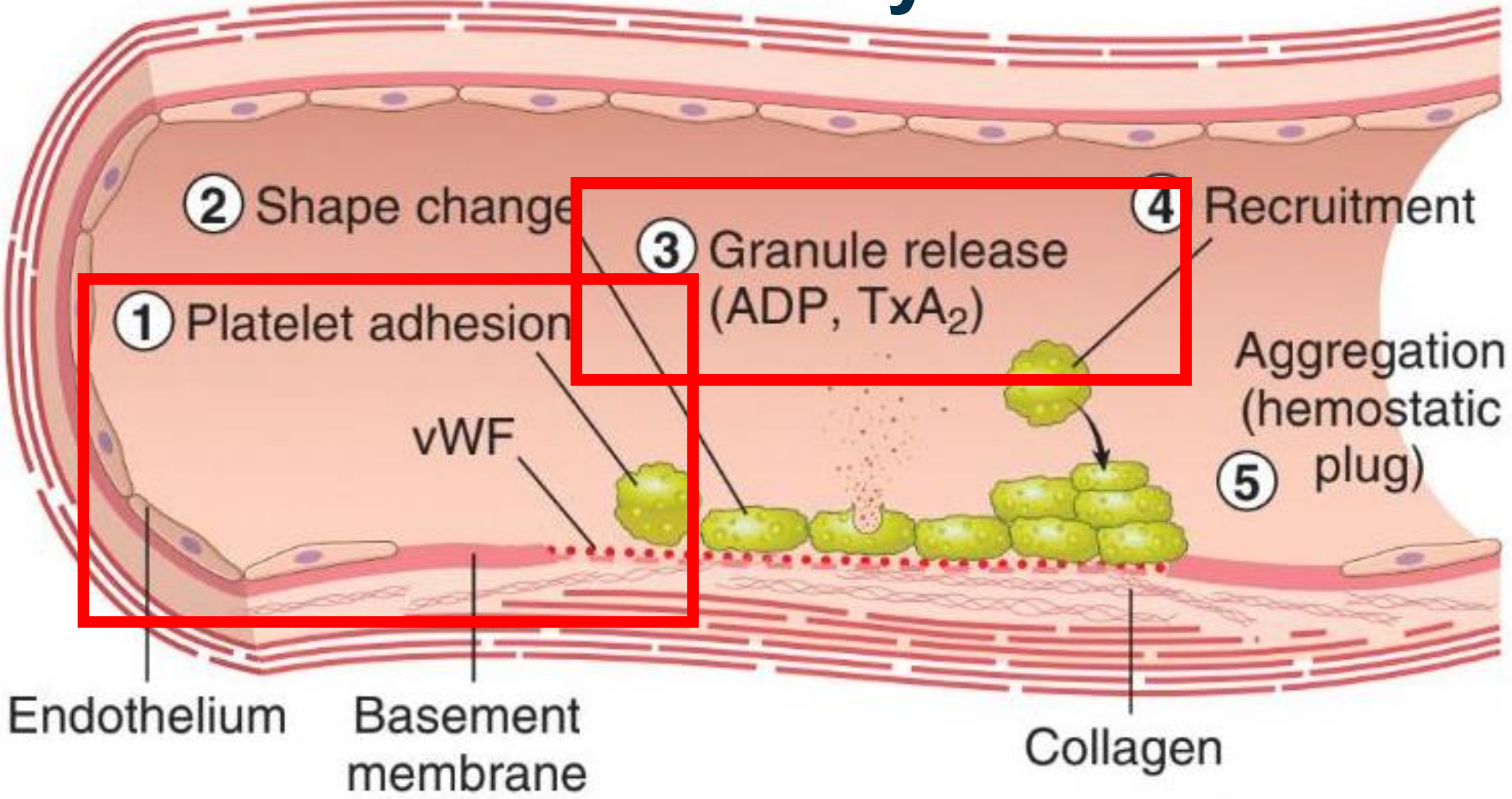
- aCL: Anticardiolipin antibodies
- ADP: Adenosine diphosphate
- AHA: American Heart Association
- Anti-β2GP1: Anti-beta-2 glycoprotein 1
- aPTT: Activated partial thromboplastin time
- APL: Antiphospholipid
- APLA: Anti Phospholipid Antibody
- APS: Antiphospholipid syndrome
- ASH: American Society of Hematology
- AT: Antithrombin
- β_2GPI: Beta-2 glycoprotein I
- CI: Confidence interval
- COC: Combined oral contraceptive
- DOAC: Direct oral anticoagulant
- dRVVT: Dilute Russell's viper venom time
- DVT: Deep vein thrombosis
- ELISA: Enzyme-linked immunosorbent assay
- FVL: Factor V Leiden
- F5 gene: Factor V gene
- HMWK: High molecular weight kininogen
- HR: Hazard ratio
- IgM: Immunoglobulin M
- IgG: Immunoglobulin G
- IL-1: Interleukin 1
- IL-6: Interleukin 6
- IL-8: Interleukin 8
- INR: International normalized ratio
- LA: Lupus anticoagulant
- LDA: Low-dose aspirin
- LMWH: Low-molecular weight heparin
- MTOR: Mechanistic target of rapamycin
- OR: Odds ratio
- PCR: Polymerase chain reaction
- PGM: Prothrombin gene mutation
- PMNs: Polymorphonuclear leukocytes
- PC: Protein C
- PS: Protein S
- PT: Prothrombin Time
- RR: Relative risk
- TF: Tissue factor
- TFPI: Tissue factor pathway inhibitor
- TxA2: Thromboxane A2
- VTE: Venous thromboembolism
- vWF: Von Willebrand factor

Outline

1. Physiology of hemostasis
2. Pathophysiology of thrombophilia
3. Epidemiology of thrombophilia
4. Thrombophilia testing guidelines
5. Treatment recommendations

1. Physiology of Hemostasis

Primary Hemostasis



Kumar V et al. *Robbins and Cotran Pathologic Basis of Disease*. 2009.

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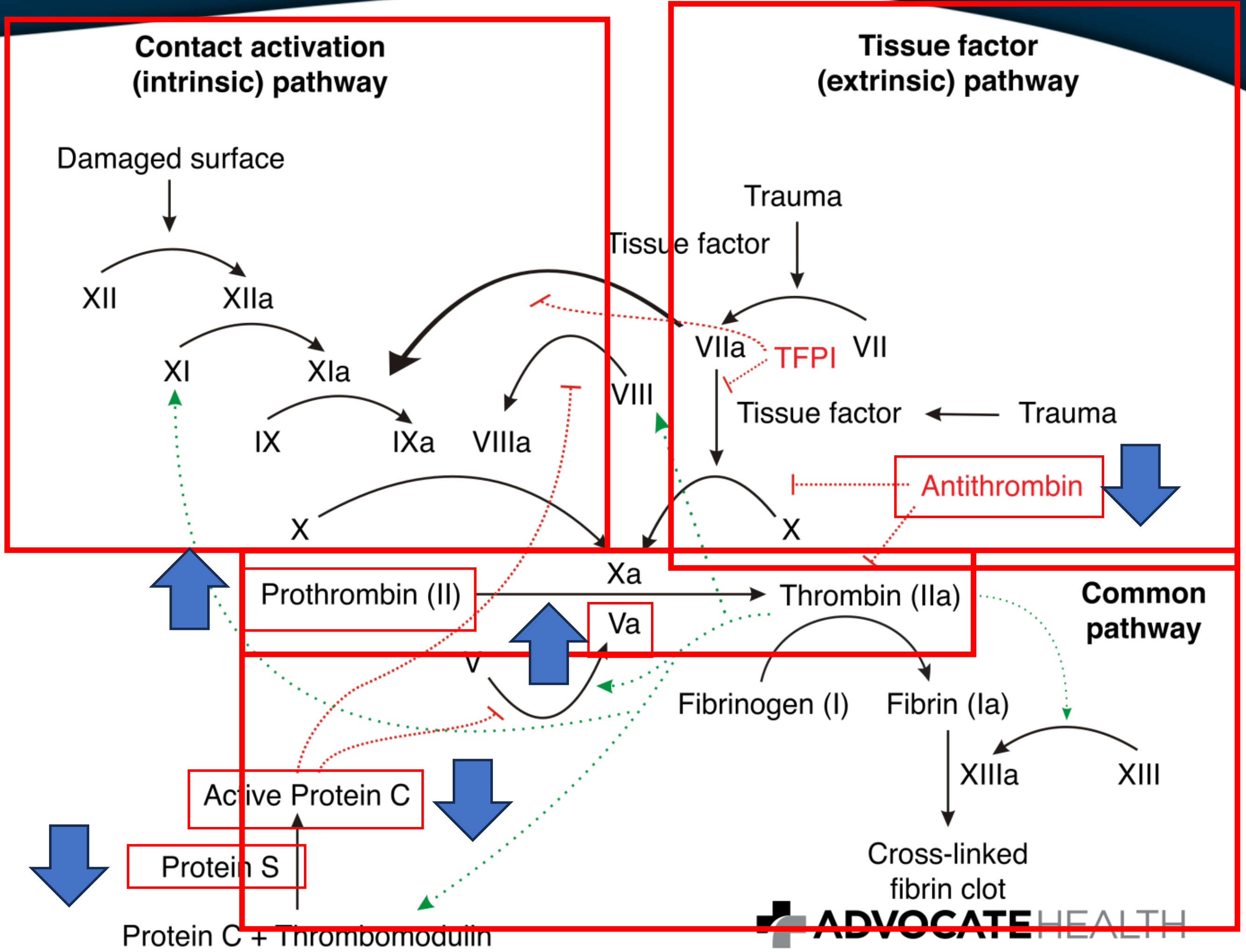
Coagulation Inhibition



MyHematology. Secondary Hemostasis. 2024.

2. Pathophysiology of Thrombophilia

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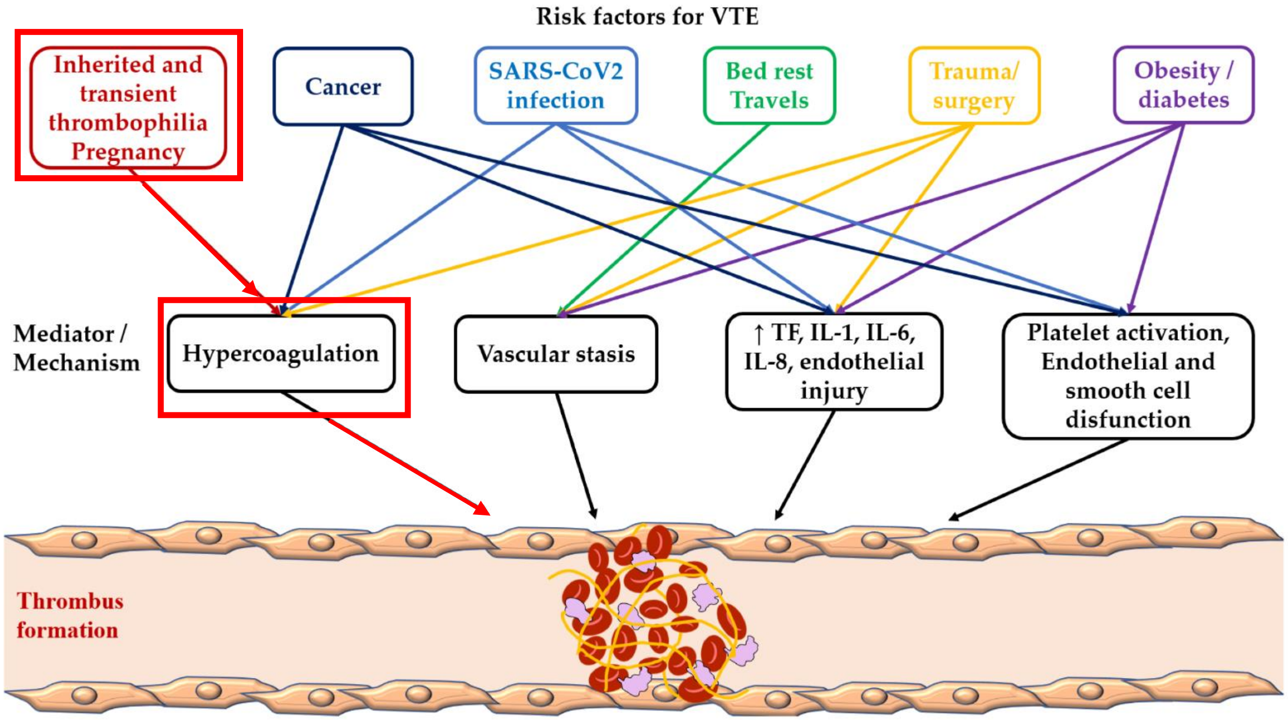
Pathophysiology of Thrombophilia



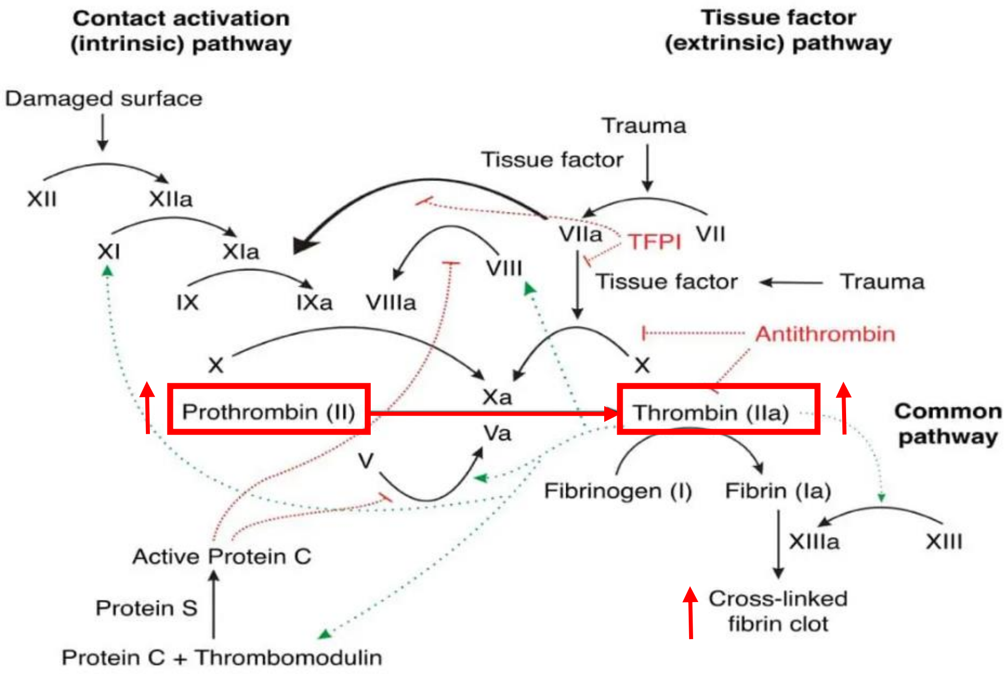
Altwayan R et al. *Transfus Clin Biol.* 2025.
Pastori D et al. *Int J Mol Sci.* 2023.

Inherited Thrombophilia

- Prothrombin gene mutation (PGM)
- Factor V Leiden (FVL)
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency

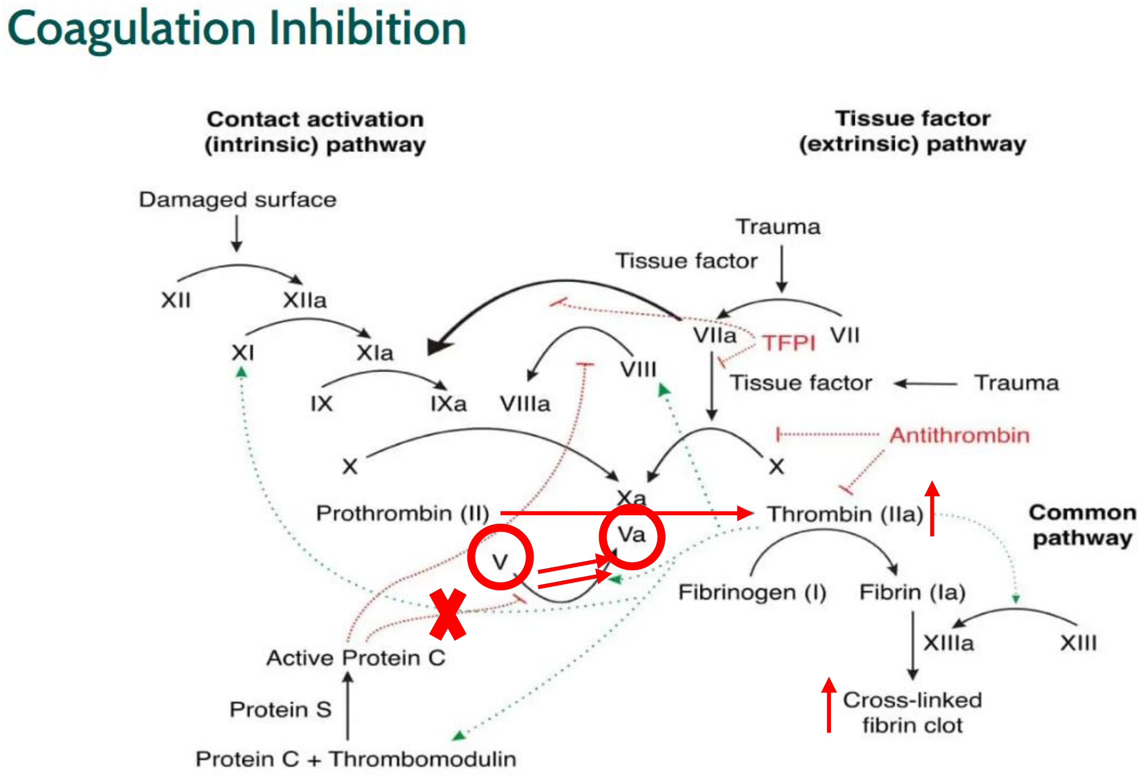
Prothrombin Gene Mutation

Coagulation Inhibition



Altwayan R et al. *Transfus Clin Biol.* 2025.
Stevens SM et al. *J Thromb Thrombolysis.* 2016.

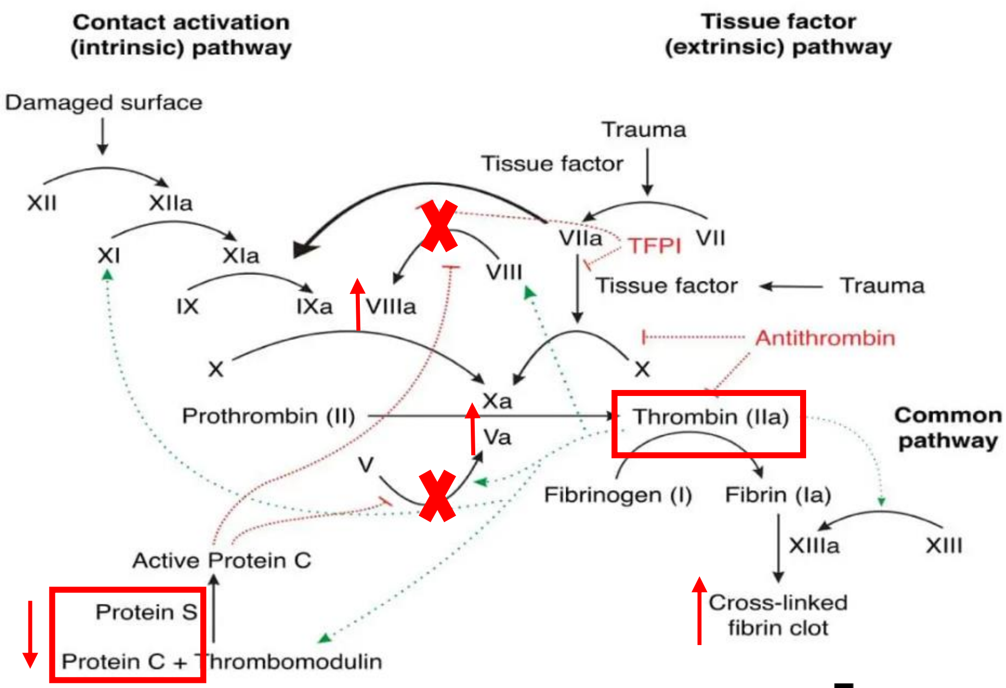
Factor V Leiden



Altwayan R et al. *Transfus Clin Biol.* 2025.

Protein C and S Deficiencies

Coagulation Inhibition



Altwayan R et al. *Transfus Clin Biol.* 2025.

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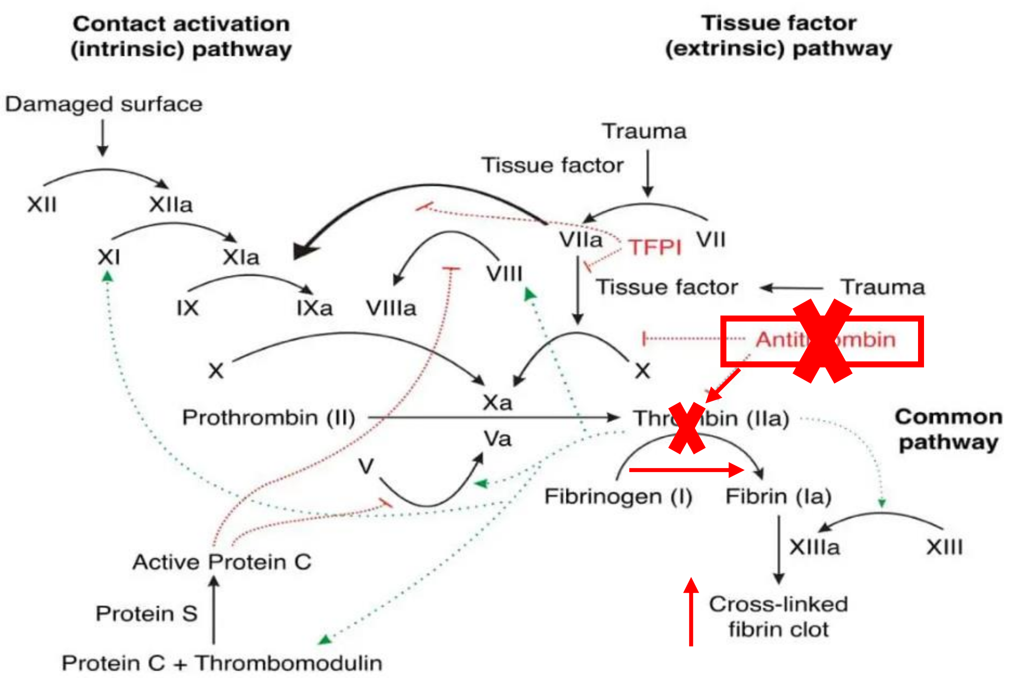
Antithrombin Deficiency

Coagulation Inhibition



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Altwayan R et al. *Transfus Clin Biol.* 2025.
Stevens SM et al. *J Thromb Thrombolysis.* 2016.

Acquired Thrombophilia

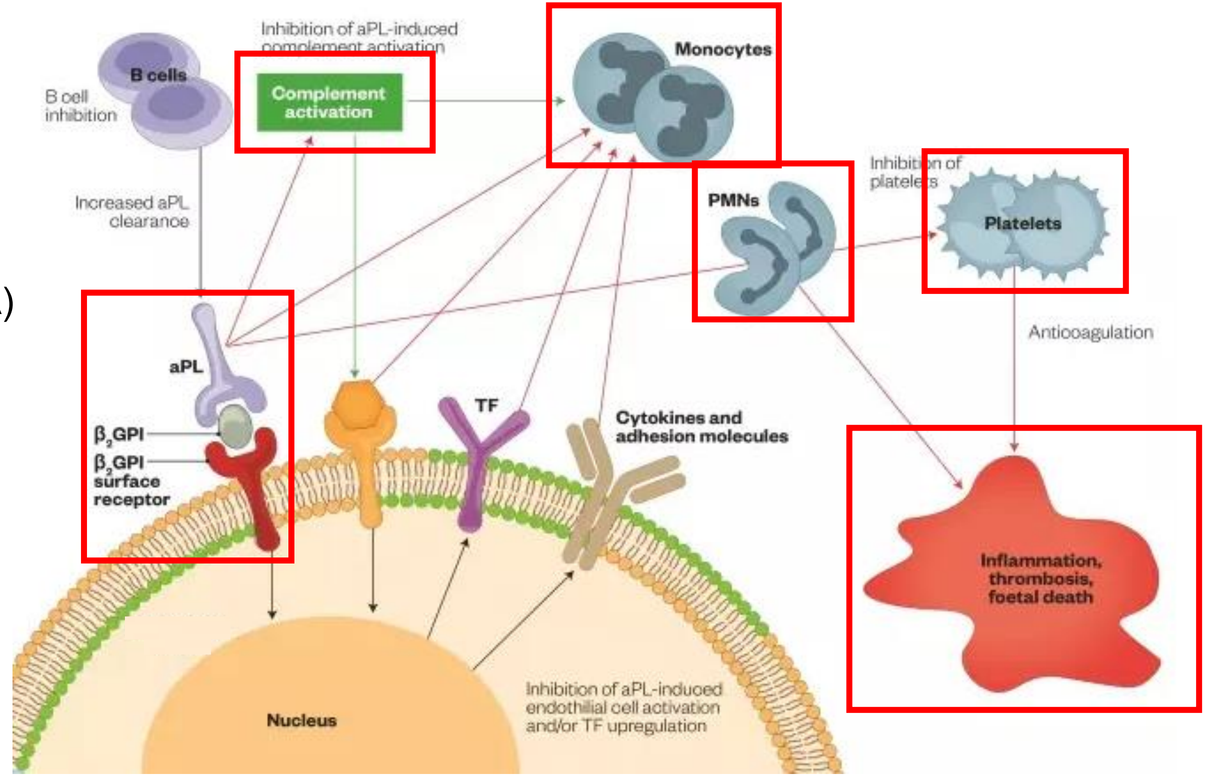
- **Autoimmune disease**
  - **Antiphospholipid syndrome**
- Prolonged hospital stays
- Pregnancy
- Cancer
- Unhealthy lifestyle habits
- Acquired versions of inherited thrombophilia

Antiphospholipid Syndrome

Lupus anticoagulant (LA)

Anticardiolipin (aCL)

Anti-β2Glycoprotein I (anti-β2GP1)



Erkan D et al. *Arthritis Rheum.* 2007.
Sammaritano LR. *Best Pract Res Clin Rheumatol.* 2020.

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Is it Lupus?

- Lupus anticoagulant (LA) is a type of antiphospholipid antibody.
- A positive LA test means a patient has the LA antibody.
- A positive LA does not mean a patient has systemic lupus erythematosus (SLE).
    - Patients with SLE may test positive for LA.

Giannakopoulos B, Krilis SA. *N Engl J Med.* 2013.

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Assessment Question #1

Which of the following are antibodies involved in antiphospholipid syndrome? (Select all that apply.)

a. Lupus anticoagulant
b. Anticardiolipin
c. Prothrombin
d. anti-β2Glycoprotein I

3. Epidemiology of Thrombophilia

Epidemiology

- Estimated 150,000 – 200,000 deaths per year from VTE in the United States of America

- Types of thrombophilia
    - Inherited thrombophilia
    - Acquired thrombophilia

- An estimated 15% of patients with VTE under the age of 45 have an inherited thrombophilia.

Altwayan R et al. *Transfus Clin Biol.* 2025.

Prothrombin Gene Mutation

Prevalence of mutation in the general population Estimated between 7 and 40 per 1000			
Relative risk for recurrence ↑	Relative Risk for first VTE ↑	Relative Risk for arterial thrombosis No consistent association	Relative Risk for pregnancy complications ↑

Middeldorp S. *Hematology ASH Educ Program.* 2016.
Middeldorp S et al. *Blood Adv.* 2023.

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Factor V Leiden

Prevalence of mutation in the general population Estimated between 3 and 7 per 100			
Relative risk for recurrence, Heterozygous ↑	Relative Risk for first VTE* ↑	Relative Risk for arterial thrombosis* ↑	Relative Risk for pregnancy complications ↑
Relative risk for recurrence, Homozygous ↑↑			

Results limited by sample size for Homozygous, known increased risk compared to Heterozygous

Middeldorp S. *Hematology ASH Educ Program.* 2016.
Middeldorp S et al. *Blood Adv.* 2023.

Protein C Deficiency

Prevalence of mutation in the general population Estimated 1 in 500			
Relative risk for recurrence ↑↑	Relative Risk for first VTE ↑↑	Relative Risk for arterial thrombosis No consistent association	Relative Risk for pregnancy complications ↑

Middeldorp S. *Hematology ASH Educ Program.* 2016.
Middeldorp S et al. *Blood Adv.* 2023.

Protein S Deficiency

Prevalence of mutation in the general population Estimated between 3 and 13 in 10000			
Relative risk for recurrence ↑	Relative Risk for first VTE * 0 - ↑↑↑	Relative Risk for arterial thrombosis No consistent association	Relative Risk for pregnancy complications ↑

*Results limited by sample size

Middeldorp S. *Hematology ASH Educ Program.* 2016.
Middeldorp S et al. *Blood Adv.* 2023.

Antithrombin Deficiency

Prevalence of mutation in the general population Estimated 1 in 5000			
Relative risk for recurrence ↑↑	Relative Risk for first VTE ↑↑↑	Relative Risk for arterial thrombosis No consistent association	Relative Risk for pregnancy complications ↑

Middeldorp S. *Hematology ASH Educ Program.* 2016.
Middeldorp S et al. *Blood Adv.* 2023.

Comparative Risk of Thrombus Recurrence of Inherited Thrombophilia

Type of Thrombophilia	Relative Risk of Recurrence
Antithrombin Deficiency	107% increased risk
Protein C Deficiency	113% increased risk
Protein S Deficiency*	30% increased risk
Factor V Leiden Heterozygous	36% increased risk
Factor V Leiden Homozygous	110% increased risk
Prothrombin Gene Mutation	34% increased risk

*Results limited by sample size

Middeldorp S. *Hematology ASH Educ Program.* 2016.
Middeldorp S et al. *Blood Adv.* 2023.

Acquired Thrombophilia

- **Autoimmune disease**
  - **Antiphospholipid syndrome**
- Prolonged hospital stays
- Pregnancy
- Cancer
- Unhealthy lifestyle habits
- Acquired versions of inherited thrombophilia

Witt DM et al. *Blood Adv.* 2018.

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Antiphospholipid syndrome

<table>
<tr><td colspan="4">Prevalence in the general population

Estimated 1 in 5000</td></tr>
<tr><td>Odds ratio for recurrence with Positive LA
↑↑↑</td><td>Odds ratio for recurrence with Positive aCL or Anti-β2GP1
↑↑</td><td>Odds ratio for arterial thrombosis
↑↑</td><td>Odds ratio for pregnancy complications
No consistent association</td></tr>
</table>

Dabit JY et al. *Curr Rheumatol Rep.* 2022.
Reynaud Q et al. *Autoimmun Rev.* 2014.

Assessment Question #2

What type of deficiency would put a patient at a baseline higher risk of clotting compared to a patient without this genetic mutation? (Select all that apply.)

a. Protein C deficiency
b. Protein S deficiency
c. Prothrombin deficiency
d. Antithrombin deficiency

4. Thrombophilia Testing Guidelines

When is it indicated to test for various types of thrombophilia?

When to screen for all types of inherited thrombophilia?

Transient risk factors for VTE	
Confined to bed for > 3 days with an acute illness	Pregnancy
Leg injury associated with decreased mobility for > 3 days	Combined Oral Contraceptives
Confined to bed rest for < 3 days with an acute illness	Confined to bed rest for > 3 days outside of hospital

Conditional recommendation to test in patients with:

- VTE provoked by nonsurgical major transient risk factor

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Middeldorp S et al. *Blood Adv.* 2023.

When to screen for all types of inherited thrombophilia?

Conditional recommendation to test in patients with:

- Cerebral venous thrombosis (CVT) or Splanchnic venous thrombosis
  - If considering stopping anticoagulation

- Active cancer patients receiving systemic therapy at low or intermediate risk for VTE, who have a family history of VTE

ASH Thrombophilia Testing. *Blood Adv.* 2023.
ASH DVT/PE Treatment. *Blood Adv.* 2020..

When to potentially screen for familial thrombophilia?

Recommendation to test if considering thromboprophylaxis or starting oral contraceptives:

- Patient has a familial history of VTE and
- Known familial thrombophilia
    - Protein C deficiency
    - Protein S deficiency
    - Antithrombin deficiency
- With minor provoking risk factors

Consider selective testing or testing for all inherited thrombophilia

ASH Thrombophilia Testing. *Blood Adv*. 2023.

When to potentially screen for familial thrombophilia?

Recommendation to **<u>Not</u>** test if considering thromboprophylaxis or starting oral contraceptives:

- Patient has a familial history of VTE and
- Known familial thrombophilia
  - Prothrombin G20210A Gene Mutation
  - Factor V Leiden
- With minor provoking risk factors

Consider selective testing or testing for all inherited thrombophilia

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Middeldorp S et al. *Blood Adv.* 2023.

When to consider testing for antiphospholipid syndrome

- Laboratory abnormalities
  - Prolonged aPTT
- Recurrent clotting on therapeutic anticoagulation
  - VTE
  - Stroke
  - TIA
- Concurrent autoimmune disease
- Early miscarriages

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Devreese KMJ et al. *J Thromb Haemost.* 2020.

Revised Sapporo Clinical Criteria

Criteria	Definition	Notes
Clinical		
Thrombosis: arterial, venous, or microthrombi	≥ 1 thrombosis	Confirmed by imaging; no significant inflammation in vessel wall
Pregnancy loss	Early: ≥3 consecutive pre-embryonic or embryonic loss at < 10 weeks Late: ≥ 1 fetal death at ≥ 10 weeks	Excludes anatomic, hormonal, and chromosomal abnormalities
Pregnancy morbidity	≥ 1 premature birth at ≤ 34 weeks due to eclampsia, severe preeclampsia, or severe placental insufficiency	

Sammaritano LR. *Best Pract Res Clin Rheumatol.* 2020.
Devreese KMJ et al. *J Thromb Haemost.* 2020.

What do thrombophilia lab tests look like?

Prothrombin Gene Mutation Testing

Test	Reference Range	Indication of Thrombophilia
PCR Prothrombin G20210A Gene Mutation	Not detected	Heterozygous or homozygous mutant

- Limitations on testing
    - Recent transfusion within 45 days
    - Allogeneic stem cell transplant
    - Differing Prothrombin gene mutation

Connors JM. *N Engl J Med.* 2017.
Zhang S et al. ACMG VTE Genetic Testing. *Genet Med.* 2018.

Factor V Testing

Test	Reference Range	Indication of Thrombophilia
Activated Protein C Resistance Assay	1.95 - 2.89 (Ratio)	< 1.95
PCR Reflex for Factor V mutation	Not detected	Heterozygous or homozygous mutant

- Limitations
  - Recent transfusion within 45 days
  - Allogeneic stem cell transplant
  - Acute thrombosis
  - Differing Factor V gene mutation
  - DOACs falsely increase protein C assay
  - Warfarin must be held 45 days for protein C assay

Adcock DM, Gosselin R. *Thromb Res.* 2015.
Connors JM. *N Engl J Med.* 2017.
Zhang S et al. ACMG VTE Genetic Testing. *Genet Med.* 2018.

Protein C Deficiency Testing

Test	Reference Range	Indication of Thrombophilia
Activated Protein C Activity Assay	70 – 140%	< 70% activity
Reflex Activated Protein C Antigen	70 - 140%	< 70% antigen in circulation

- Limitations for activity testing
  - Recent transfusion within 45 days
  - Allogeneic stem cell transplant
  - Acute thrombosis
  - DOACs falsely increase protein C assay
  - Warfarin decreases both activity and antigens, must be held 45 days prior to testing

Adcock DM, Gosselin R. *Thromb Res.* 2015.
Connors JM. *N Engl J Med.* 2017.
Moser KA, Smock KJ. *Hematology ASH Educ Program.* 2021.

Protein S Deficiency Testing

Test	Reference Range	Indication of Thrombophilia
Activated Protein S Activity Assay	70 – 140%	< 70% activity
Reflex Activated Protein S, Total Antigen	70 - 140%	< 70% antigen in circulating bound and free antigen
Reflex Activated Protein S, Free Antigen	70 - 140%	< 70% unbound free antigen

- Limitations for activity testing
  - Recent transfusion within 45 days
  - Allogeneic stem cell transplant
  - Acute thrombosis
  - DOACs falsely increase protein S assay
  - Warfarin decreases both activity and antigens, must be held 45 days prior to testing

Adcock DM, Gosselin R. *Thromb Res.* 2015.
Connors JM. *N Engl J Med.* 2017.
Moser KA, Smock KJ. *Hematology ASH Educ Program.* 2021.

Antithrombin Deficiency Testing

Test	Reference Range	Indication of Thrombophilia
Antithrombin Activity Assay	80 – 124%	< 80% activity
Reflex Antithrombin Antigen level	> 80%	< 80% antigen in circulation

- Limitations on activity testing
  - Recent transfusion within 45 days
  - Allogeneic stem cell transplant
  - Acute thrombosis
  - Unfractionated Heparin based on Thrombin assay
  - LMWH based on Xa assay
  - DOACs overestimation of activity based on Xa or Thrombin Assay

Adcock DM, Gosselin R. *Thromb Res.* 2015.
Connors JM. *N Engl J Med.* 2017.
Moser KA, Smock KJ. *Hematology ASH Educ Program.* 2021.

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Antiphospholipid Syndrome Testing:

Lupus Anticoagulant

Screening test: Standard aPTT or dRVVT

If prolonged

→

Confirmation test: Mixing study with pooled normal plasma

If ratio does not correct

→

Confirmation test: Hexagonal phase phospholipid

If ratio does not correct

→

Lupus Anticoagulant

Positive (repeat test 12 weeks apart)

Connors JM. *N Engl J Med.* 2017.
Favaloro EJ et al. *Res Pract Thromb Haemost.* 2024.
Tektonidou MG et al. *Ann Rheum Dis.* 2019.
Tripodi A et al. *J Thromb Haemost.* 2020.

Antiphospholipid Syndrome Testing

Test	Reference Range	Indication of Thrombophilia
Lupus Anticoagulant	Not detected	Positive

- Limitations to testing
  - Acute thrombotic episode
  - Warfarin
  - Unfractionated Heparin
  - LMWH
  - DOACs

Connors JM. *N Engl J Med.* 2017.
Favaloro EJ et al. *Res Pract Thromb Haemost.* 2024.
Tektonidou MG et al. *Ann Rheum Dis.* 2019.
Tripodi A et al. *J Thromb Haemost.* 2020.

Testing for LA while on Anticoagulation

- Warfarin
  - May have effect through aPTT or dRVVT
  - Mixing study attempts to correct confounding variables in lab
  - Recommendation to stop 1-2 weeks prior and bridge with LMWH

- DOACs
  - May have effect through aPTT or dRVVT
  - Lab assay contains neutralizer, but effects limited
  - Recommendation to stop 48 hours and test at trough

Favaloro EJ et al. *Res Pract Thromb Haemost.* 2024.
Tripodi A et al. *J Thromb Haemost.* 2020.
Devreese KMJ et al. *J Thromb Haemost.* 2020.

Testing for LA while on Anticoagulation

- UFH
  - May have effect through aPTT, dRVVT or TT
  - Lab assay contains neutralizer, but effects limited
  - Recommendation to draw 4-8 hours after discontinuing

- LMWH
  - May have effect through aPTT or dRVVT
  - Lab assay contains neutralizer, but effects limited
  - Recommendation to draw 12 hours after last dose of LMWH

Favaloro EJ et al. *Res Pract Thromb Haemost.* 2024.
Tripodi A et al. *J Thromb Haemost.* 2020.
Devreese KMJ et al. *J Thromb Haemost.* 2020.

Antiphospholipid Syndrome Testing

Test	Reference Range	Indication of Thrombophilia
Anticardiolipin antibody (aCL), IgG	< 40 Units	> 40 Units
Anticardiolipin antibody (aCL), IgM	< 40 Units	> 40 Units
Anti-Beta-2 Glycoprotein 1 antibody, IgG	Below local lab cut off	> 99th Percentile of cut off
Anti-Beta-2 Glycoprotein 1 antibody, IgM	Below local lab cut off	> 99th Percentile of cut off

- Limitations
  - Acute infection
  - Malignancy

Connors JM. *N Engl J Med.* 2017.
Tektonidou MG et al. *Ann Rheum Dis.* 2019.

APS: Revised Sapporo Classification

Criteria	Definition	Notes
Laboratory (1 positive test and a repeat postive test at least 12 weeks apart)		
Lupus anticoagulant	Prolonged PL-dependent coagulation test: aPTT, dRVVT recommended	Failure to correct on mixing with normal platelet-poor plasma and correction with adding excess PL
Anticardiolipin IgG, IgM	≥ 40 IgM or IgG phospholipid units	aβ2GPI-dependent ELISA
Anti-β2Glycoprotein I IgG, IgM	≥ 99^{th} percentile	Standard aβ2GPI ELISA
Clinical		
Thrombosis: arterial, venous, or microthrombi	≥ 1 thrombosis	Confirmed by imaging; no significant inflammation in vessel wall
Pregnancy loss	Early: ≥3 consecutive pre-embryonic or embryonic loss at < 10 weeks Late: ≥ 1 fetal death at ≥ 10 weeks	Excludes anatomic, hormonal, and chromosomal abnormalities
Pregnancy morbidity	≥ 1 premature birth at ≤ 34 weeks due to eclampsia, severe preeclampsia, or severe placental insufficiency	

Sammaritano LR. *Best Pract Res Clin Rheumatol.* 2020.
Devreese KMJ et al. *J Thromb Haemost.* 2020..

APS: aPL Risk Classification

- Low-risk antibody profile:
  - Isolated aCL or aβ2GPI at a low to medium titer
- High-risk antibody profile (one of the following):
  - Presence of LA
  - Double positive aPL:
    - Any combination of LA, aCL, and aβ2GPI
  - Triple positive aPL:
    - Positive for all three aPL antibodies: LA, aCL, and aβ2GPI)
- High-risk aPL is specifically notable with high aCL or aβ2GPI titers
- Catastrophic APS:
  - Thrombosis in 3 or more organs within 7 days

Pengo V et al. *J Thromb Haemost.* 2010.
Garcia D, Erkan D. *N Engl J Med.* 2018.

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Thrombophilia Disease State and Lab Interactions

Antithrombin deficiency	Antiphospholipid syndrome
○ No direct effect on aPTT ○ Can see "Heparin Resistance" or low aPTT with heparin use ▪ aPTT is accurate, but requires larger doses to reach therapeutic ○ Can consider switching to LMWH and monitor anti-Xa levels	○ Falsely prolongs aPTT ○ Falsely prolongs point of care PT ○ Recommend to monitor heparin with anti-Xa levels or switch to LMWH

Croles FN et al. *Thromb Res.* 2019.
Mittal P et al. *Hematology ASH Educ Program.* 2024.

Assessment Question #3

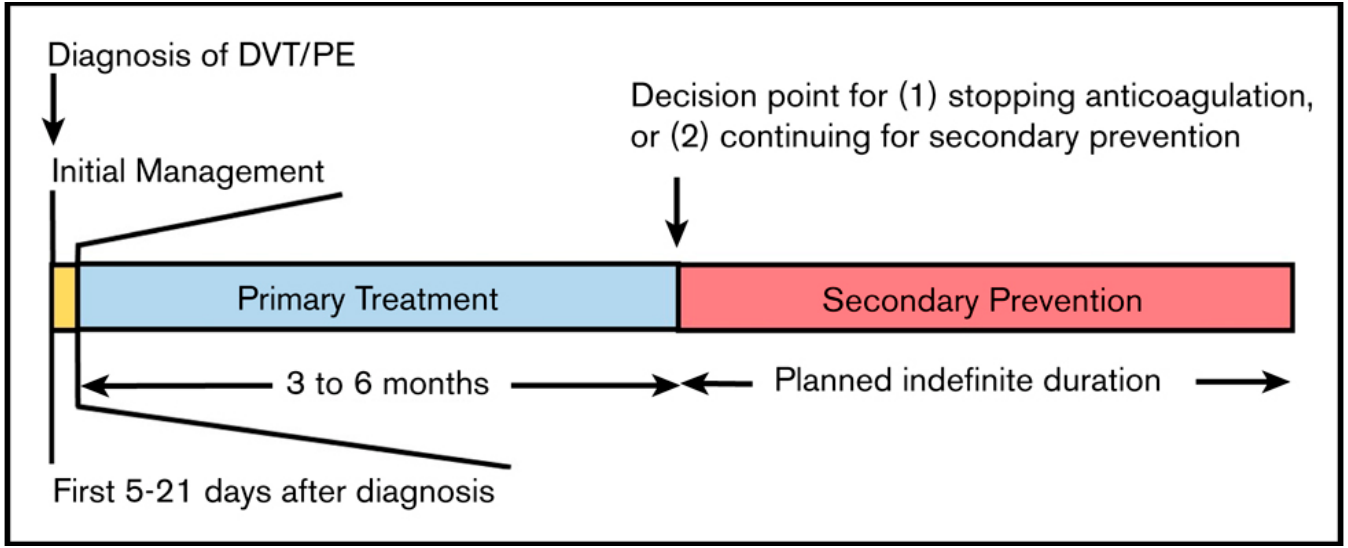
Based off the lab results what type of inherited thrombophilia does this patient have?

Lab Test	Result	Reference Range
Activated Protein C Resistance	2.34	1.95 - 2.89
Protein C Activity	79%	70 – 140%
Protein C Antigen	89%	70 – 140%
Protein S Activity	40%	65 – 140%
Protein S, Total Antigen	60%	70 – 140%
Protein S, Free Antigen	45%	70 – 140%
Prothrombin Gene Mutation PCR	Not Detected	

a. Protein C deficiency
b. Factor V Leiden
c. Prothrombin Gene Mutation
d. Protein S deficiency

5. Treatment Recommendations

Anticoagulation Overview



Witt DM et al. *Blood Adv.* 2018.
Ortel TL et al. *Blood Adv.* 2020.

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Anticoagulation Overview: Secondary Prevention

- Indefinite secondary prevention (prophylaxis) after first 6 months of treatment should be considered when:
  - In VTE provoked by a chronic (persistent) risk factor
  - In unprovoked VTE
  - In recurrent unprovoked VTE
- Must also consider factors that increase bleed risk:
  - Older age/ frequent falls
  - History of bleeding
  - Cancer/ thrombocytopenia
  - Hepatic or renal insufficiency
  - Concurrent antiplatelet therapy
  - History of stroke

Ortel TL et al. *Blood Adv.* 2020.

Anticoagulation Overview

Drug/Class	Example Drugs	Place in Therapy	Considerations
DOACs	Apixaban	VTE treatment Secondary prophylaxis	No recommendation for one over another, but kidney function may impact decision.
	Rivaroxaban		
	Dabigatran		
	Edoxaban	VTE treatment	
Direct factor Xa inhibitors (parenteral)	Fondaparinux	VTE treatment Secondary prophylaxis	Use as an alternative to heparins; prophylaxis contraindicated in patients < 50 kg; not recommended in pregnancy.

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Ortel TL et al. *Blood Adv.* 2020.

Anticoagulation Overview

Drug/Class	Example Drugs	Place in Therapy	Considerations
Vitamin K antagonist	Warfarin	VTE treatment Secondary prophylaxis	Contraindicated in pregnancy
Heparins	Enoxaparin (LMWH) Unfractionated heparin	Primary prophylaxis VTE treatment	LMWH is recommended over unfractionated heparin in pregnancy
Low-dose aspirin (antiplatelet)	Aspirin 81 mg	Primary prophylaxis (off-label)	Not recommended over anticoagulants.

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Ortel TL et al. *Blood Adv.* 2020.

Treatment of Inherited Thrombophilia

Primary Prophylaxis		
Type of thrombophilia	**Recommended agents**	**Evidence for recommendation**
Prothrombin gene mutation	No treatment (may consider in high-risk situations)	ASH 2020 VTE Guidelines
Factor V Leiden		
Protein C deficiency		
Protein S deficiency		
Antithrombin deficiency		

Stevens SM et al. *J Thromb Thrombolysis.* 2016.
Ortel TL et al. *Blood Adv.* 2020.

Treatment of Inherited Thrombophilia

Acute Management		
Type of thrombophilia	**Recommended agents**	**Evidence for recommendation**
Prothrombin gene mutation	Heparin/ LMWH DOACs Warfarin	ASH 2020 VTE Guidelines
Factor V Leiden		
Protein C deficiency		
Protein S deficiency		
Antithrombin deficiency		

Stevens SM et al. *J Thromb Thrombolysis.* 2016.
Ortel TL et al. *Blood Adv.* 2020.

Treatment of Inherited Thrombophilia

Secondary Prevention (Indefinite)		
Type of thrombophilia	**Recommended agents**	**Evidence for recommendation**
Prothrombin gene mutation	DOACs Warfarin	ASH 2020 VTE Guidelines (Risk-benefit analysis)
Factor V Leiden		
Protein C deficiency		
Protein S deficiency		
Antithrombin deficiency		

Stevens SM et al. *J Thromb Thrombolysis.* 2016.
Ortel TL et al. *Blood Adv.* 2020.

Treatment of Inherited Thrombophilia

- Special Considerations:
  - Antithrombin deficiency:
    - May use antithrombin III replacement in addition to anticoagulation
    - In patients with heparin resistance, argatroban is recommended as an alternative parenteral agent
  - Protein C deficiency:
    - Use of DOACs is recommended over warfarin due to potential for Warfarin-Induced Skin Necrosis

Zwicker JI et al. *J Thromb Haemost.* 2020.
Parsi K et al. *Australas J Dermatol.* 2003.

Antithrombin III Replacement

- Antithrombin III is a blood product that directly replaces the protein, antithrombin, back into the blood.
- Dosed using the following formula:
  - [(desired antithrombin level % - baseline antithrombin level %) x body weight (kg)] / 1.4 = units of antithrombin required
  - Initial dose should raise antithrombin levels to 120%
- Used in addition to anticoagulation for individuals who:
  - Have high-risk VTE such as cerebral vein or cerebral sinus thrombosis
  - Develop VTE and for whom an adequate aPTT cannot be reached (helps to overcome heparin resistance)

Zwicker JI et al. *J Thromb Haemost.* 2020.
Levy JH, Connors JM. *N Engl J Med.* 2021.

Warfarin-Induced Skin Necrosis

- Rare thrombohemorrhagic skin condition with high morbidity
- Caused by an imbalance of procoagulant and anticoagulant factors
- When protein C levels are low, there is a greater imbalance
  - Specifically seen due to the short half-life of protein C (14 hours)
- Results in thrombotic occlusions of microvasculature leading to necrosis
- Use of warfarin in homozygous protein C deficiency can be fatal
- Management: surgical debridement of necrotic tissue
- DOACs are recommended as the alternative treatment

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Parsi K et al. *Australas J Dermatol.* 2003.

Treatment of Antiphospholipid Syndrome

Primary Prophylaxis		
Recommended agents	**Specific patient considerations**	**Evidence**
No treatment	No history of thrombosis or obstetric APS	APLASA study (2007)
Aspirin 81 mg	History of obstetric APS High-risk aPL profile	2019 EULAR recommendations Arnaud et al. (2014)
Hydroxychloroquine	Patients with SLE	2019 EULAR recommendations

Erkan D et al. *Arthritis Rheum.* 2007.
Tektonidou MG et al. *Ann Rheum Dis.* 2019.
Arnaud L et al. *Autoimmun Rev.* 2014.

Aspirin for primary thrombosis prevention in the antiphospholipid syndrome (APLASA study)

- Multicenter, randomized, double-blind, placebo-controlled trial
- Asymptomatic, persistently aPL-positive patients
- n = 98 patients
- Randomized 1:1 to receive either aspirin 81 mg daily or placebo
- Results:
  - Thrombosis occurred in:
    - 2.75 per 100 patient-years in the aspirin group
    - 0 per 100 patient-years in the placebo group experienced acute thrombosis
  - HR: 1.04 (95% CI 0.67-1.54; p = 0.91)
- Conclusion: Low-dose aspirin did not show benefit over placebo in preventing acute thrombosis.

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Erkan D et al. *Arthritis Rheum.* 2007.

Arnaud et al. (2014)

- Meta-analysis that included 11 studies of patients with aPL
- Patients were treated for primary prophylaxis using low-dose aspirin
- Pooled odds ratio (OR) for the risk of first thrombosis:
  - OR: 0.50, $I^2 = 46\%$, $p = 0.03$
- Subgroup analysis showed a protective effect of low-dose aspirin against arterial but not venous thrombosis:
  - Arterial thrombosis OR: 0.48 (95%CI: 0.28–0.82)
    - $I^2 = 3\%$
    - $p = 0.007$
  - Venous thrombosis OR: 0.58 (95% CI: 0.32–1.06)
    - $I^2 = 0\%$
    - $p = 0.08$
- Conclusion: Low-dose aspirin may be beneficial in patients with APS

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Arnaud L et al. *Autoimmun Rev*. 2014.

Treatment of Antiphospholipid Syndrome

Acute Management		
Recommended agents	**Patient population**	**Evidence for recommendation**
Heparin (UFH or LMWH)	Initial treatment while bridging Pregnant patients	ASH 2020 VTE Guidelines
Warfarin (INR 2-3)	Arterial thrombosis, systemic rheumatic disease, or prior history of APS	ASH 2020 VTE Guidelines
DOACs	Transient aPL positivity due to acute infection, provoked VTE, cardiovascular risk factors in patients with arterial thrombosis	Theorized only

Stevens SM et al. *J Thromb Thrombolysis.* 2016.
Ortel TL et al. *Blood Adv.* 2020.

Can we use DOACs?

- In most cases, DOACs are **not** recommended to treat VTE in patients with APS.
- May be considered in patients with:
  - Transient aPL positivity due to acute infection
  - Provoked VTE
  - Cardiovascular risk factors in patients with arterial thrombosis
- In these patients, the thrombotic event was likely not caused by APS.

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Stevens SM et al. *J Thromb Thrombolysis.* 2016.

Treatment of Antiphospholipid Syndrome

Secondary Prevention (Indefinite)		
Recommended agents	**Patient population**	**Evidence for recommendation**
Warfarin (INR 2-3)	VTE Arterial thrombosis	2018 AHA Stroke Guidelines (Class 2a Recommendation) 2026 AHA PE Guidelines (Class 1 Recommendation) TRAPS trial ASTRO-APS trial
Warfarin (INR 3-4)	Arterial thrombosis with high risk of recurrence Recurrent thromboses	EULAR recommendations (WAPS Trial)

Powers WJ et al. *Stroke.* 2019.
Pengo V et al. *J Thromb Haemost.* 2010.
Woller SC et al. *Blood Adv.* 2022.
Creager MA et al. *Circulation.* 2026.

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TRAPS Trial (2018)

- Randomized open-label multicenter noninferiority, blinded endpoint study
- Included high-risk, triple-positive aPL patients
- n = 120 patients
- Randomized 1:1 to receive either rivaroxaban 20 mg daily or warfarin with an INR goal of 2-3
- Trial was terminated early due to an excess of thromboembolic events in the rivaroxaban group

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Pengo V et al. *J Thromb Haemost.* 2010.

ASTRO-APS Trial (2022)

- Multicenter prospective randomized open-label, blinded endpoint study
- Included patients with a history of thrombosis due to APS
- n=48 patients
- Randomized 1:1 to receive either apixaban 2.5 mg twice daily or warfarin with an INR goal of 2-3
  - After the 13^{th} patient was randomized, patients with prior arterial thrombosis were excluded
  - After the 25^{th} patient was randomized, apixaban was increased to 5 mg twice daily
- Study was terminated early due to an excess of stroke occurring in the apixaban group

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Woller SC et al. *Blood Adv.* 2022.

Treatment of APS

Secondary Prevention (Indefinite)		
Recommended agents	**Patient population**	**Evidence for recommendation**
DOACs	Single venous thrombosis and low-risk aPL profile	2026 AHA PE Guidelines (Class 2b Recommendation)
LMWH	Pregnant patients Recurrent thromboses	CHEST Guidelines

Creager MA et al. *Circulation.* 2026.
Bates SM et al. *Chest.* 2012.

Assessment Question #4

Based on current treatment recommendations, which of the following treatments is recommended for an aPL-positive patient with no history of VTE but a high-risk aPL profile?

a. No treatment
b. Low-dose aspirin
c. Warfarin
d. DOAC

Summary/Conclusion

- Thrombophilia is a rare condition characterized by hypercoagulability requiring therapeutic anticoagulation
- Routine testing for thrombophilia is not recommended
- Treatment recommendations are based on a combination of thrombotic events and additional risk factors.

Additional Reference Slides

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2023 ASH Guidelines on Thrombophilia Testing

Population	Recommendation	Level of Evidence
Unprovoked VTE	Do not test for thrombophilia	Conditional
VTE provoked by surgery	Do not test for thrombophilia	Conditional
VTE provoked by nonsurgical major transient risk factor	Test for thrombophilia, and indefinite anticoagulant treatment for patients with thrombophilia	Conditional
VTE provoked by pregnancy or postpartum	Test for thrombophilia, and indefinite anticoagulant treatment for patients with thrombophilia	Conditional
VTE associated with use of Combined oral contraception	Test for thrombophilia, and indefinite anticoagulant treatment for patients with thrombophilia	Conditional
An unspecified type of VTE (not specified as provoked or unprovoked VTE	Do not test for thrombophilia	Conditional

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Middeldorp S et al. *Blood Adv.* 2023.

2023 ASH Guidelines on Thrombophilia Testing

Population	Recommendation	Level of Evidence
Cerebral venous thrombosis (CVT) Or Splanchnic venous thrombosis	a) In the settings when anticoagulation would otherwise be discontinued after primary short-term treatment: test for thrombophilia, and indefinite anticoagulant treatment for patients with thrombophilia b) In settings when anticoagulation would otherwise be continued indefinitely: do not test for thrombophilia	Conditional
Individuals with a family history of VTE and known thrombophilia		
Heterozygous Factor V Leiden or heterozygous Prothrombin G20210A	Do not test for thrombophilia	Conditional
Protein C, S or antithrombin deficiency	Test for the thrombophilia known in the family or test for all hereditary thrombophilia and use thromboprophylaxis in individuals with thrombophilia	Conditional
Family history of VTE and unknown thrombophilia status	Do not test for thrombophilia	Conditional

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Middeldorp S et al. *Blood Adv.* 2023.

2023 ASH Guidelines on Thrombophilia Testing

<table>
<tr><th colspan="2">Population</th><th>Recommendation</th><th>Level of Evidence</th></tr>
<tr><td colspan="2">Women from the general population considering COCs</td><td>Do not test for thrombophilia</td><td>Strong</td></tr>
<tr><td rowspan="2">Women with known family history of VTE and thrombophilia and considering COCs</td><td>Factor V Leiden or Prothrombin 20210A</td><td>Do not test for thrombophilia</td><td>Conditional</td></tr>
<tr><td>Protein C, S or antithrombin deficiency</td><td>Test for thrombophilia and avoid COCs in women with thrombophilia</td><td>Conditional</td></tr>
<tr><td colspan="2">Ambulatory patients with cancer who are classified to be at low or intermediate risk for VTE, who have a family history of VTE in first-degree relatives</td><td>Test for all hereditary thrombophilia and use thromboprophylaxis in individuals with thrombophilia</td><td>Conditional</td></tr>
</table>

Middeldorp S et al. *Blood Adv.* 2023.

Summary of Anticoagulation effects on inherited testing

Lab assay	Heparin	LMWH	Warfarin	DOACs
Activated Protein C resistance	-	-	↓	↑
Factor V Leiden PCR	-	-	-	-
Prothrombin gene mutation PCR	-	-	-	-
Antithrombin Activity	↑	↑	-	↑
Antithrombin Antigen	-	-	-	-
Activated Protein C activity	-	-	↓	↑
Activated Protein C antigen	-	-	↓	-
Activated Protein S activity	-	-	↓	↑
Activated Protein S antigen, Total/Free	-	-	↓	-

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